UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/416,735	10/13/1999	ISABELLA A. ATENCIO	CJ-0897Q	6563

7590 11/04/2002

RICHARD B MURPHY
CANJI INC
3525 JOHN HOPKINS COURT
SAN DIEGO, CA 92121

EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/04/2002 16

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/416,735	ATENCIO ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2001 and 14 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7 and 21-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7 and 21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed August 14, 2002 (Paper No. 15) has been entered. The response filed June 19, 2001 (Paper No. 7) has been entered into the file. However, the amendment set forth therein was not entered for the reasons set forth on the Notice of Non-Compliant Amendment mailed June 25, 2002 (Paper No. 8). The amendment filed August 14, 2002 (Paper No. 15) corrects the error. Claims 5 and 7 have been amended. Claims 21-36 have been newly added.

Accordingly, Claims 5-7 and 21-36 remain pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-7 stand rejected and Claims 21-31 and 33-36 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action of Paper No. 5 (mailed 2/16/01), because the specification, while being enabling for an *in vitro* method of increasing the infectivity of a cell to a viral vector by treatment of the cell with a micro-calpain inhibitor, does not reasonably provide enablement for an *in vivo* method of increasing the infectivity of a cell to a viral vector by treatment of the cell with a micro-calpain inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for increasing the infectivity of a cell to a viral vector by treatment of the cell with a micro-calpain inhibitor. The claims encompass both *in vitro* and *in vivo* applications of the method.

At pages 5-6 of the response (response of June 19, 2001, Paper No. 7, hereinafter referred to as "the response"), Applicants argue that individuals have been treated with viral vector vaccines for more than 50 years. However, it is unclear how this argument addresses the grounds of rejection, as the invention does not relate to vaccination and the rejection does not discuss vaccination. Furthermore, no support is offered for this assertion, so it is unclear what Applicants are attempting to argue. Applicants go on to argue that the gene therapy agent ONYX-015/dl1520 is entering Phase III clinical trials. However, the existence of a Phase III clinical trial is not an indicator that gene therapy is a predictable art. On the contrary, successful gene therapy protocols have been developed only with painstaking effort and intensive investigation.

At page 6, paragraph 2 of the response, Applicants argue that the present invention is not claiming a method of treating a human being with a viral vector, but rather enhancing the infectivity of the cells to the viral vector. Applicants assert that whether or not the viral vector employed provides a therapeutic benefit to the individual is collateral to the patentability of the present invention. However, it is well-established that claimed invention must satisfy the utility requirement. The only utility asserted in the specification is for use of the claimed method as an adjunct to gene therapy. See the specification at page 4, lines 1-35, which discusses p53 gene therapy and the use of the claimed method as an adjunct to this gene therapy protocol. As such, the claimed invention must be enabled for use with a wide range of gene therapy applications, and the specification must provide specific guidance teaching how to effect that use. Moreover, the specification should teach how to use the claimed protocol to achieve increased infectivity of cells for a broad range of viral vectors. With regard to Claims 22-27, 30, 31, 35, and 36, it is clear that the intended use of the method is to provide a therapeutic effect. Furthermore, with regard to

in vivo applications of the claimed method, the specification must teach how to use the claimed method for *in vivo* applications to achieve the claimed result of increased infectivity. In other words, the specification must provide guidance sufficient to teach the skilled artisan **how to carry out the administration of a micro-calpain inhibitor to achieve the claimed effect of increased infectivity.** For reasons of record, the specification does not teach how to use the claimed method *in vivo*.

At page 7 of the response, Applicants argue that the Examiner has expanded the claim of the present invention to require that increased infectivity result in enhanced therapeutic benefit. With regard to Claims 5-7, Applicants are incorrect in this interpretation. If the specification provided an enabling disclosure teaching how to use the claimed method *in vivo* to achieve increased infectivity over the broad scope of the claim, use of the claimed method in gene delivery protocols that do not involve production of a therapeutic effect would be considered a useful application of the claimed method. However, for reasons of record the specification, does not teach how to use the claimed method *in vivo* to achieve increased infectivity. With regard to Claims 22-31 and 33-35, Applicant is correct in their interpretation, because recitation of a therapeutic gene necessarily imparts to the claimed invention an intended use for therapy. There is no utility disclosed for achieving increased infectivity in the absence of an enhanced therapeutic benefit. The **only** utility asserted in the specification is that the method of achieving increased infectivity can be used as an adjunct to gene therapy. By not making a rejection under 35 U.S.C. 101, the Examiner has acknowledged that this is a credible utility, albeit one that is not enabled by the instant specification. **Enablement** is then evaluated for the **only utility asserted in the specification.** For reasons of record, the specification fails to provide an enabling disclosure teaching how to use the claimed method *in vivo* to achieve increased infectivity. If the increased infectivity is just that and nothing more, then the utility requirement has not been satisfied. Applicants seem to be arguing that the increased infectivity is itself a useful endpoint and the Examiner does not accept this argument because the increased infectivity clearly must coincide with a desired effect, such as increased transgene

expression or an enhanced therapeutice effect. Ample reasons have been provided to doubt that the invention can be practiced *in vivo* without undue experimentation.

At page 7, part C of the response, Applicants argue that the rejection under 35 U.S.C. 112, first paragraph is improper because the Examiner has not addressed enablement but rather the utility requirement of 35 U.S.C. 101. As discussed above, by not making a rejection under 35 U.S.C. 101, the Examiner has acknowledged that the utility asserted in the specification is a credible utility, albeit one that is not enabled by the specification. However, the specification fails to teach how to use the claimed method to achieve increased infectivity *in vivo*. It is well-established that the enablement requirement relates to **both** how to make and how to use the claimed invention. The rejection under 35 U.S.C. 112, first paragraph is not grounded on a "lack of utility" basis, but rather is based on a lack of teaching how to use the claimed invention for the only utility asserted in the specification. By not imposing a utility rejection under 35 U.S.C. 101, the Examiner acknowledges that a credible utility exists for the claimed invention. In this case, that utility, as asserted in the specification, is gene therapy (see the specification at page 4, lines 1-35; page 9, line 18 through page 10, line 6, and throughout). However, the instant specification fails to provide an enabling disclosure teaching how to use the claimed invention *in vivo* in a manner that achieves increased infectivity, wherein the increased infectivity leads to an enhanced therapeutic result. Moreover, the specification fails to even teach how to use the claimed invention in a manner that achieves increased infectivity alone. Increased infectivity is a claim limitation, but the specification does not teach how to use the claimed method in a manner that achieves this effect. The MPEP specifically addresses this situation. According to the MPEP § 2164.07, section II, titled WHEN UTILITY REQUIREMENT IS SATISFIED, "[i]n some instances, the use will be provided, but the skilled artisan will not know how to effect that use. In such a case, no rejection will be made under 35 U.S.C. 101, but a rejection will be made under 35 U.S.C. 112, first paragraph. As pointed out in *Mowry v. Whitney*, 81 U.S. (14 Wall.) 620 (1871), an invention may in fact have great utility, i.e., may be "a

highly useful invention," but the specification may still fail to "enable any person skilled in the art or science" to use the invention. 81 U.S. (14 Wall.) at 644."

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

In the instant case, it is clear that further teachings are required to allow the skilled artisan to practice the claimed invention. Given that the state of the art is unpredictable, for reasons of record, the skilled artisan would have been required to engage in undue experimentation to practice the claimed invention *in vivo* and achieve the claimed result.

At page 8 of the response, Applicants argue that when administered *in vivo*, the calpain inhibitor has an anti-tumor effect. However, this issue has already been addressed in the Office Action of Paper No. 5 (mailed 2/16/01); demonstration of an anti-tumor effect is not sufficient to enable the **claimed** invention which is specifically directed to **increasing infectivity of cells to viral vectors.** The specification demonstrates that **the calpain inhibitor alone has anti-tumor activity** in the absence of any viral vector. Thus, the demonstration of an **anti-tumor effect** in the presence of viral vector is not a measurement of **infectivity,** but rather is an expected effect of a compound with **known anti-tumor activity.** The experiments described in the specification do not measure cellular infectivity. No assays were performed to determine the **infectivity** of the cells in the presence and absence of CI-1. On the contrary, administering two agents, each with known anti-tumor activity, to a xenografted tumor produced the very much expected result of enhanced anti-tumor activity when the two agents were used together as compared to each agent used separately.

At page 9 of the response, Applicants argue that "[i]n the absence of some soundly based reason to question whether or not the invention will work as claimed, the Examiner is bound to accept the Applicants assertion of utility." As discussed above, the Examiner does accept the asserted utility as a credible utility, albeit one that is not enabled by the instant specification. No less than six references have been cited to support a finding of unpredictability in the art. Moreover, the court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970). Ample reasons have been provided to doubt that the invention can be practiced *in vivo* without undue experimentation. The *in vivo* studies described in the specification demonstrate enhanced cell death, **not increased infectivity.** Applicants' own work suggests that this effect may be limited to tumor cells, not broadly applicable to any cell type. See page 6 of the Office Action of Paper No. 5 (mailed 2/16/01) which quotes Atencio et al. (2000) for disclosing that "[b]ecause calpain inhibitors have been used in a variety of pathological indications to protect cell from death ..., we believe the enhancement of cell death observed in this study may be specific for tumor cells" (p. 251, column 2, paragraph 3 of Atencio et al., 2000). Since the administration of CI-1 alone produces the desired effect of limiting tumor growth, this effect is obviously **independent of any alleged increase in infectivity of the cells.**

At page 10 of the response, Applicants argue that the Examiner has improperly characterized the present invention as gene therapy. On the contrary, it is Applicants' own specification that asserts that the claimed method should be used as an adjunct to gene therapy (see specification at page 4, lines 1-35; page 9, line 18 through page 10, line 6, and throughout).

At page 10 of the response, Applicants refer to "some rather outdated review articles cited by the Examiner." The priority date of this application is October 1998. Three of the articles cited to support unpredictability in the art were published in 1997. Contentions that the articles are old are not impressive

absent a showing that the art advanced so radically in the year following their publication so as to reverse the state of the art of gene therapy from one that is highly unpredictable to one that is predictable. Applicants have not offered any support for their assertion that the articles are outdated. The cited references are clearly representative of the state of the art at the time the invention was made.

Given the limited working examples, the limited guidance in the specification, the broad scope of the claims, and the unpredictability of using the claimed methods to achieve the claimed effect or as an adjunct to gene therapy applications, undue experimentation would have been required for one skilled in the art to practice the claimed methods *in vivo* to achieve the claimed effect of increased infectivity.

Allowable Subject Matter

Claim 32 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE BAKER
PATENT EXAMINER